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(54) Title: SUBSTANCE DEPENDENCE TREATMENT USING OPIATE ANTAGONISTS AND SEROTONIN COMPOUNDS

(57) Abstract

Patients are treated for alcohol, marijuana, cocaine, opiate and polysubstance dependency by administration of combination of an effective amount of an opioid antagonist such as nalmefene, naloxone, naltrexone, or a mixture of any of these, and a serotonergic medication, such as sertraline, fluoxetine, paroxetine, fluvoxamine, or odansetron. Administration of an effective amount of an opioid antagonist alone helps to prevent relapse after detoxification is complete, and addition of the serotonergic medication increases the effectiveness, decreases the side effects of the opioid antagonist, and also helps relieve effects of withdrawal.

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SUBSTANCE DEPENDENCE TREATMENTS USING OPIATE ANTAGONISTS AND SEROTONIN COMPOUNDS

Related Application Data

This application claims priority benefit of U.S. patent application serial number 60/046,162, filed 20 May 1997.

Technical Field of the Invention

This invention relates to the use of opioid antagonists such as naltrexone or nalmephene with serotonergic medication for substance dependence, to increase abstinence rates, reduce relapse once abstinence has been achieved, and to diminish side effects associated with the use of opiate antagonists.

Background of the Invention

Drug dependence continues to be a major health hazard for millions of Americans, and causes significant social and emotional problems in the families and associates of the dependent individual.

Dependence is an adaptive biological state induced by chronic drug exposure manifesting itself in various behavioral and physiological responses when drug exposure ceases. Withdrawal from alcohol following chronic use results in the emergence of an abstinence syndrome which reaches its peak intensity within the first few days. Cessation of alcohol consumption has been shown to result in a

number of signs and symptoms of withdrawal such as increases in irritability, anxiety, restlessness, impatience, somatic complaints including nausea, insomnia, and tremulousness, and increases in heart rate and blood pressure as well as hallucinations and seizures, all of which are collectively called the alcohol withdrawal syndrome. Similarly, cessation of cocaine and opiate use also results in significant withdrawal symptomatology, while cessation of marijuana use results in a more subtle withdrawal syndrome.

Following completion of detoxification, during the treatment phase craving for the substance of abuse and depression are cited as the major reasons for relapse. Some research studies have documented the existence of a protracted withdrawal syndrome which is prevalent for months following completion of detoxification and consists of signs and symptoms such as depression, anxiety, altered sleep, and hyperexcitability (Satel, *et al., American Journal of Psychiatry*, 1993, *150*: 695-704).

In recent years, research efforts have focused on medication strategies to treat withdrawal as well as long term strategies to treat dependence. For example, naltrexone alone has been found to increase abstinence and reduce relapse to heavy drinking in alcohol dependence, above that of placebo. Abstinence has been increased by naltrexone from approximately 25% to 50% over a 3 month period, and relapse to heavy drinking has been reduced from 50% to 25% over the same period. Following up at 6 months post cessation of naltrexone, there is a tendency for the naltrexone treated subjects to drink less than the non naltrexone group but not to the same extent immediately following treatment. However, not all alcohol dependent individuals benefit from naltrexone therapy and strategies to maximize treatment outcome are needed. In addition, approximately 10% of alcohol dependent individuals who start naltrexone treatment experience severe side effects similar to the withdrawal symptomatology described above that leads them to discontinue treatment, suggesting that new strategies be developed. Therefore, it would be desirable to have alternate additive treatments to help alcohol cessation,

to prevent or help symptoms of alcohol withdrawal, and to prevent relapse after alcohol withdrawal. Similarly, although naltrexone is approved for the treatment of opiate dependence, it is not considered an effective treatment for most people because compliance is so poor, presumably in part because naltrexone continues provoke subclinical signs and symptoms of opiate withdrawal even in the detoxified opiate addict. A new approach to opiate antagonist therapy that would be more tolerable would be of considerable value. At this time, the most widely used therapy for opiate addiction is methadone maintenance, an expensive therapy to administer and one that is not well accepted by many communities because of the addictive nature of methadone. Finally, there are absolutely no pharmacotherapies available at this time for the treatment of marijuana abuse and cocaine dependence, and other psychological therapies have limited effectiveness.

Summary of the Invention

It is an objective of the invention to provide a new treatment for substance abuse and dependence cessation including alcohol, cocaine, marijuana, opiates and polysubstance abuse.

It is a further and more specific objective of the invention to provide a substance abuse cessation treatment that yields optimal substance abuse cessation rates.

It is another objective of the invention to provide a method for minimizing symptoms of withdrawal on cessation of substance abuse.

It is an additional objective of the invention to provide a method for preventing relapse after completion of detoxification.

These and other objectives are provided by the present invention which provides a method for decreasing symptoms of withdrawal, reducing side effects and increasing abstinence after cessation of substance abuse, and preventing relapse after cessation of substance intake, by administration of an effective amount of an opioid antagonist such as nalmefene, naloxone, naltrexone, or a mixture of any of these, in combination with a serotonergic medication such as sertraline, fluoxetine, fluvoxamine, paroxetine, or odansetron. Naltrexone is used in one embodiment.

Detailed Description of the Invention

This invention is based upon the finding that opioid antagonists in combination with serotonergic medications are useful in alcohol cessation treatments and in marijuana cessation, in cessation of cocaine, opiates and polysubstance abuse.

In the practice of the invention, effective amounts of opioid antagonists alone are employed in treatments for alcoholism or other substance abuse disorders. Any opioid antagonist may be employed; naltrexone and/or related compounds are used in some preferred embodiments, but any other class of opioid antagonists may be used instead or in addition. Naltrexone, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxymorphinan-6-one, is a congener of naloxone, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)morphinan-6-one, having opiate-blocking activity. Naltrexone related compounds include, but are not limited to, other structurally related opiate antagonists including naloxone, nalmefene (5ß-17-(cyclopropylmethyl)-4,5-epoxy-6-methylenemorphinan-3,14-diol), and mixtures thereof. Naltrexone is used in one embodiment; nalmefene, in another.

Administration of opioid antagonists or opioid antagonists in conjunction with other compounds can be local or systemic, or a combination of therapies.

Systemic administration is preferred in some embodiments. Systemic administration can be via any method known in the art such as, for example, oral administration of lozenges, tablets, capsules, granules, or other edible compositions; intravenous, intramuscular, or intradermal administration, *e.g.*, by sterile injections, including depot versions; implants; parenteral administration of fluids, and the like.

For local administration, an antagonist or a compound mixture are typically topically applied to the skin or mucosa in association with a pharmaceutically acceptable carrier in which the antagonist is dispersed or solubilized. Carriers may be aqueous compositions, lotions, creams, ointments, soaps, and the like.

The serotonergic medications described can be any one of a number of serotonergic medications including sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, zimeldine, viqualine, fenfluramine, d-fenfluramine, buspirone, gepirone, odansetron and/or other related compounds. Administration of serotonergic medications or of serotonergic medications in conjunction with other compounds can be local or systemic, or a combination of therapies. Systemic administration is preferred in some embodiments. Systemic administration can be via any method known in the art and summarized above.

For local administration, a serotonergic medication or a compound mixture are typically topically applied to the skin or mucosa in association with a pharmaceutically acceptable carrier in which the antagonist is dispersed or solubilized such as that described for administration of the opioid antagonists described. Carriers may be aqueous compositions, lotions, creams, ointments, soaps, and the like.

Naltrexone and/or related compounds are administered to a patient in amounts effective to reduce reinforcement from alcohol, cocaine, marijuana and

opiates and polysubstance abuse during detoxification, and/or to prevent relapse after completion of detoxification. The amount of compound necessary to reduce reinforcement and prevent relapse during the therapeutic treatment of withdrawal, or to prevent relapse following detoxification is not fixed *per se*, and necessarily is dependent upon the severity and extent of substance dependence, the particular compound employed, and the method of administration. In some embodiments, the compound is taken orally as a Revia(r)™ tablet. Typical doses vary from about 25 mg to about 100 mg, more narrowly from about 25 mg to about 150 mg daily, more narrowly from about 25 mg to about 100 mg. In one embodiment, smaller doses such as up to about 25 mg are employed. These compounds could be used to prevent relapse to use in alcohol, cocaine, opiate and marijuana abuse and polysubstance abuse.

Serotonergic medications can also be administered in combination with opiate antagonists to treat symptoms of withdrawal, and to help treat relapse, and to increase abstinence. Typical doses vary from about 25 mg to 200 mg for sertraline, 10 mg to about 60 mg for fluoxetine, 25 mg to 200 mg for fluvoxamine, 10 mg to 50 mg for paroxetine, 10 mg to 60 mg for citalopram, 15 mg to 120 mg for fenfluramine or d-fenfluramine, and 5 mg to 60 mg of buspirone. These combinations could be used to prevent relapse to heavy use in alcohol, cocaine, opiate, and marijuana abuse and polysubstance abuse.

In some embodiments, the dependent individual is first placed on the serotonergic compound for a period of time, *e.g.*, 1 to 7 days in one embodiment, and is then begun on naltrexone or the opiate antagonist. Alternatively, the dependent individual is placed on the initial dose of the opioid antagonist for a brief period. Naltrexone treatment may begin at either about 12.5 mg a day with increases up to about 50 mg after a week, or initially at levels of about 50 mg. Lower doses of about 12.5 or 25 mg may also be used throughout the entire treatment. Subsequently, a dose of the serotonergic medication could be added to the naltrexone regime and increased in dose to tolerance for a period from about 3

to 4 to about 12 months, the period of highest risk of relapse following complete detoxification. In another embodiment, both compounds are begun simultaneously. The optimal sequence and dose for beginning therapy with naltrexone and the serotonergic compound might be made on the basis of clinical research experience.

Although the effects of alcohol in the central nervous system have long been recognized, the precise mechanisms involved in centrally mediated responses to alcohol are not fully understood. This is particularly true for its addictive property. While not wishing to be bound to any theory, it may be that the method of the invention functions because some of the reinforcing effects of different substances of abuse including alcohol, marijuana and cocaine are mediated via activation of the endogenous opioid system, and the serotonergic system.

Alcoholism. In alcoholism, opiate antagonists have been shown to reduce alcohol self-administration in monkeys (50% dose-dependent reduction over placebo; Altshuler, *et al., Life Sciences*, 1980, *26*: 679-688) and rats bred for high and low alcohol preference (Froehlich, *et al., Alcohol and Alcoholism*, 1987, (Suppl. 1): 333-337). A significant benefit from the opiate antagonist naltrexone has been found in the treatment of alcohol dependent humans over 12 weeks in 2 large outpatient trials. Naltrexone in conjunction with psychotherapy produced a significant rise in complete abstinence from alcohol and a significant fall in relapse to heavy drinking (O'Malley, *et al.*, 1995, *25*: 681-689). Although the majority of researchers found that opiate antagonists reduce alcohol preference, not all studies have done so. For example, one researcher found an increase in alcohol consumption in hamsters given a single dose of naltrexone (Ross, *et al., Proceedings of the Western Pharmacological Society*, 1976, *19*: 326-330).

The serotonin system has also been implicated in the pathogenesis of alcoholism. Numerous animal studies have suggested a serotonin deficiency in alcohol consuming animals and a large number of human experiments have

suggested a serotonergic deficiency in alcoholics relative to non alcoholics (Farren, *Journal of Serotonin Research*, 1995, *1*: 9-26). In general, increased serotonin activity decreases alcohol intake and decreased serotonin function increases alcohol intake. The specific serotonin reuptake inhibitors, including fluoxetine, fluvoxamine, citralopram and zimeldine have all been found to reduce alcohol consumption in alcohol preferring lines of rats (Murphy, *et al., Alcohol*, 1993, *2*: 349-352). Sertraline, a selective serotonin reuptake inhibitor, has been shown to significantly reduce the intake of alcohol in non-alcohol preferring male rats (Gill, *et al., Alcohol*, 1988, *5*: 349-354). On the other hand, efforts to use serotonergic agents to treat alcohol dependence in humans has met with much less success than that shown in animals.

Serotonergic reuptake inhibitors including zimeldine, citralopram, viqualine and fluoxetine have shown very small decreases (9 - 15%) in alcohol consumption in non alcohol dependent humans (Naranjo, *et al., Clinical Pharmacology and Therapeutics* 1990, *47*: 490-498). In alcohol dependent patients, however, serotonin reuptake inhibitors such as fluoxetine, fluvoxamine, and dex-fenfluramine have shown benefit in reducing alcohol consumption (Kranzler, *et al., Journal of Substance Abuse Treatment* 1993, *10(3)*: 283-287; Gorelick and Pardes, *Alcoholism: Clinical and Experimental Research*, 1992, *16(2)*: 261-265; Romach, *et al., Alcoholism: Clinical and Experimental Research,* 1996, *20* (Suppl. 2), Abst #520). In one open clinical trial, sertraline in combination with counseling has been shown to help reduce alcohol consumption in seven non depressed subjects with alcohol abuse or dependence (George, *et al., Presentation at Research Society on Alcoholism Annual Meeting*, Hawaii, June 1994), but these findings have not been replicated or extended to a large clinical trial and the contribution of the medication to the reduction in drinking cannot be disentangled from the effect of counseling. Based on a recent review of the literature, Saitz and O'Malley (in J.H. Samet, *et al.*, eds., *Medical Clinics of North America*, 1997, *81(4)*: 881-907) concluded that the SSRI's have no value in the treatment of nondepressed alcoholics.

Cocaine. A number of preclinical studies document the efficacy of naltrexone in the treatment of cocaine abuse (Bilsky, *et al., Life Sciences*, 1992, *50*: 85-90; Corrigall, *et al., Psychopharmacology*, 1991, *104*: 167-170). Conversely, some experiments have shown no benefit of naltrexone in cocaine self administration in rats (Carroll, *et al., Journal of Pharmacology and Experimental Therapeutics*, 1986, *238*: 1-7). Clinical assessments of cocaine abuse in treatment seeking opiate dependent subjects indicate that treatment with the opiate agonist methadone was associated with substantially more cocaine abuse when compared with treatment with the opiate antagonists naltrexone or buprenorphine, suggesting that methadone treatment may be "priming" cocaine use, while naltrexone treatment via blocking reinforcement may be attenuating cocaine use (Kosten, *et al., Life Sciences*, 1989, *44*: 887-892). In one experiment disulfiram reduced the alcohol consumption of alcohol and cocaine abusing individuals by helping reduce their alcohol abuse, although naltrexone was not as successful (Carroll, *et al., American Journal on Addictions*, 1993, *2*: 77-79).

The serotonergic system has also been investigated with regards to cocaine abuse. Cocaine is a powerful serotonin reuptake inhibitor and chronic cocaine administration results in decreased 5-HT transmission, and this has been suggested as an explanation for the depressive symptoms of acute cocaine withdrawal (Cunningham, *et al., Annals of the New York Academy of Sciences*, 1992, *654*: 117-127). Sertraline has been used, along with fluoxetine, in open label studies of cocaine abusers and has shown promise in decrease of cocaine craving, cocaine use and psychosocial function (Batki, *et al., Journal of Clinical Psychopharmacology*, 1993, *13*: 243-250).

Marijuana. Cannabis (marijuana) is one of the most widely used drugs throughout the world and currently there are no successful pharmacotherapies to treat marijuana dependence. The psychoactive component of marijuana, tetrahydrocannabinol (THC) produces a number of pharmacological effects in the CNS similar to those produced by opiates such as morphine including antinociception,

hypothermia, respiratory depression, inhibition of locomotor activity and intestinal motility. Moreover, opioid antagonists have been shown to block some of the pharmacological effects of THC. Preclinical studies have shown that, like alcohol, opiates (morphine) and other drugs of abuse, the reinforcing effects of THC are mediated by release of dopamine in the brain dopamine reward pathway. Moreover, others have shown that release of dopamine by THC can be blocked by the opioid antagonist naloxone, suggesting a role for the endogenous opioid peptides in modulating THC reinforcement similar to that documented above for alcohol dependence (Chen, *et al., Psychopharmacology*, 1990, *102*: 156-162). THC also suppresses precipitated abstinence in morphine dependent rats and has also been shown to modulate brain opioid receptors (mu and delta) at pharmacologically relevant concentration.

All the above evidence is suggestive of an opioid component in marijuana dependence similar to that seen in alcohol dependence. Therefore, agents such as naltrexone which have been used successfully to reduce alcohol self-administration could also be used in marijuana cessation treatments. However, opioid antagonists have also been shown to precipitate withdrawal in marijuana dependent rats (Kaymakcalary, *et al., Phychopharmacology*, 1988, *55*: 243) suggesting that the use serotonergic agents to reduce withdrawal and opioid antagonists to reduce reinforcement may optimize treatment of marijuana dependence. Preclinical studies also document the existence of enhanced serotonergic transmission in THC dependent animals.

The studies suggest that the opiate and serotonin system are involved in dependence on drugs of abuse. While the role of opiate antagonists in the treatment of alcohol dependence and opiate dependence is established, the evidence for the use of serotonergic medications alone is much less clear. The possibility that the combined use of opiate antagonists and serotonergic has received very limited investigation. In an animal study, a combination of the opioid antagonist naltrexone and the serotonin-3 receptor antagonist ondansetron was a reducer of self

administered alcohol intake greater than either drug alone, in both rats and mice (Le and Sellers, *Alcohol and Alcoholism*, 1994, Supplement 2, 545-549). In the second study, 25 heroin addicts were treated with naltrexone and half also received fluoxetine, presumably for depression. After six months of treatment, the group which received both showed a better retention rate in treatment (Maremmani, *et al., American Journal on Addictions*, 1995, *4*: 267-271). No data is presented about drug use or side effects; the study was not randomized, and the subjects receiving fluoxetine were presumably being treated for co-morbid depression, an accepted indication for fluoxetine.

The results described in the examples below show that a combination of opioid antagonist naltrexone and serotonergic uptake inhibitor sertraline are superior as an alcohol cessation treatment than naltrexone alone. Importantly, these results were obtained in a sample of nondepressed alcoholics. In addition, the results also describe a reduction in side effects of medication in the naltrexone and sertraline combination group. Results described in another example show that naltrexone and the serotonergic uptake inhibitor sertraline led to cessation of marijuana use in two patients.

It is an advantage of the invention that abstinence from alcohol, marijuana, opiate, cocaine abuse, and polysubstance abuse and prevention of relapse to heavy use is enhanced by this combination of medications.

The invention has very important implications for successful treatment of alcohol withdrawal and for successful treatment of long term alcohol dependence. Currently a significant number of alcoholics are not helped in their treatment by the use of an opioid antagonist such as naltrexone, and suffer significant side effects from this medication. Many individuals do not maintain complete abstinence and then relapse to heavy drinking. Naltrexone and a serotonergic medication together should enhance compliance and be more effective in encouraging abstinence and preventing relapse to heavy drinking.

In addition, the invention is useful for developing appropriate strategies for using opioid antagonists in combination with other agents in the treatment of alcoholism.

It is another advantage of the invention, that opioid antagonists with serotonin agents are useful with other substance abuse disorders involving alterations of the endogenous opioid system and the serotonergic system, or any other disorder, including non substance abuse related disorder, that has these abnormalities.

The following examples are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard.

Examples

Example 1

Nine subjects were recruited with DSM III R alcohol dependence, and received naltrexone and sertraline, a selective serotonin antagonist for a ten-week period. During this period, there were significant improvements in drinking-related outcomes. Specifically, in the days prior to treatment, subjects drank on 53.8% of these days, but during treatment they drank only 2.7% of the days. Furthermore, the average quantity of alcohol consumed per drinking day was 15.9 drinks prior to treatment, and only 1.7 drinks during treatment with naltrexone and sertraline. In addition, the subjects were compared with 9 subjects who received naltrexone alone for 10 weeks. The subjects in both groups were matched according to gender, family history of alcoholism, age, and the number of drinking days in the previous 90, and by the average drinks per drinking occasion. Over the course of the 10 week trial the naltrexone/sertraline group showed greater improvement than the naltrexone alone group. Only 44% of the naltrexone

alone group remained abstinent for the duration of the trial, compared with 67% of the naltrexone/sertraline group; 56% of the naltrexone alone group did not relapse to heavy drinking, compared to 78% of the naltrexone/sertraline group; and the number of drinking occasions was higher for the naltrexone group (7.2 vs. 1.9). In addition, subjects who received naltrexone/sertraline reported fewer side effects compared to the naltrexone alone group. There also was an increased retention in the study in the combination medication group, with the combination group staying an average of 20 days longer in the trial.

Example 2

The use of marijuana in 2 subjects who were marijuana dependent as well as alcohol dependent was monitored over a ten week period with the use of naltrexone 50 mg and with sertraline, 50 mg. Both subjects had marijuana positive urine screens at the beginning of the trial period, and had weekly urine screens performed. By week 4 both subjects reported complete cessation of use of marijuana which was verified by negative urine screens for marijuana.

The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

The papers cited herein are expressly incorporated in their entireties by reference.

The invention was made with partial government support under NIH grant numbers K02-AA-00107 and K12-OA-00167. The government has certain rights in the invention.

CLAIMS

1. A method for treating a person for alcohol dependence comprising administration to the person of an effective amount of an opioid antagonist, and an effective amount of at least one other compound that enhances the alcohol treatment.

2. A method according to claim 1 wherein the opioid antagoinst is selected from the group consisting of nalmefene, naloxone, naltrexone, and a mixture of any of these.

3. A method according to claim 1 wherein the one other compound is selected from among compounds that alter serotonin function selected from the group consisting of sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, zimeldine, viqualine, fenfluramine, d-fenfluramine, buspirone, gepirone, wellbutrin, and ondansetron.

4. A method for treating a person for marijuana dependence comprising administration to the person of an effective amount of an opioid antagonist, and an effective amount of at least one other compound that enhances the marijuana treatment.

5. A method according to claim 4 wherein the opioid antagoinst is selected from the group consisting of nalmefene, naloxone, naltrexone, and a mixture of any of these.

6. A method according to claim 4 wherein the one other compound is selected from among compounds that alter serotonin function selected from the group consisting of sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, zimeldine, viqualine, fenfluramine, d-fenfluramine, buspirone, gepirone, wellbutrin, and ondansetron.

7. A method for treating a person for cocaine dependence comprising administration to the person of an effective amount of an opioid antagonist, and an effective amount of at least one other compound that enhances the cocaine treatment.

8. A method according to claim 7 wherein the opioid antagoinst is selected from the group consisting of nalmefene, naloxone, naltrexone, and a mixture of any of these.

9. A method according to claim 7 wherein the one other compound is selected from among compounds that alter serotonin function selected from the group consisting of sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, zimeldine, viqualine, fenfluramine, d-fenfluramine, buspirone, gepirone, wellbutrin, and ondansetron, and other similar medication.

10. A method for treating a person for treating a person for polysubstance abuse comprising administration to the person of an effective amount of an opioid antagonist, and an effective amount of at least one other compound that enhances the polysubstance abuse treatment.

11. A method according to claim 10 wherein the opioid antagoinst is selected from the group consisting of nalmefene, naloxone, naltrexone, and a mixture of any of these.

12. A method according to claim 10 wherein the one other compound is selected from among compounds that alter serotonin function selected from the group consisting of sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, zimeldine, viqualine, fenfluramine, d-fenfluramine, buspirone, gepirone, wellbutrin, and ondansetron.

13. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an opioid antagonist and another compound to attenuate craving and relapse.

14. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an agent that alters serotonin function and an opioid antagonist to reduce the side effects of the opioid antagonist.

15. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an agent that alters serotonin function in order to improve compliance with the opioid antagonist.

16. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an agent that alters serotonin function in order to improve retention in treatment with the opioid antagonist.

17. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an agent that alters serotonin function in order to reduce substance abuse withdrawal symptomatology.

18. A method according to claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 wherein the person is treated with an agent that alters serotonin function in order to prevent the occurrence of withdrawal symptomatology in response to opiate antagonist treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10289

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/44
US CL : 514/282, 812, 252, 321, 419, 654, 810, 811
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/282, 812, 252, 321, 419, 654, 810, 811

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,486,362 A (KITCHELL et al) 23 January 1996, col. 1, lines 16-35; Table 1; col. 3, lines 45-52.	1-3 --- 4-18
Y	US 5,114,976 A (NORDEN) 19 May 1992, col. 6, lines 46-68; col. 7, lines 21-67; col. 11, lines 1-29; table 1; col. 9, lines 35- 67; col. 10, lines 29-33.	4-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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